ICF Consulting Review of NPB AEL Recommendation Proposed by SLR International Corporation

Introduction

ICF Consulting has been asked to review an analysis conducted by SLR International Corporation (2001) in which an acceptable exposure limit (AEL) was calculated for n-propyl bromide (NPB). In the SLR analysis, benchmark dose-response modeling was conducted using data sets for several endpoints taken from the various animal toxicity tests that have been conducted with NPB. The lower bounds of the benchmark dose (BMDLs) were then used to estimate an AEL. ICF has reviewed this report and summarizes the findings below.

Findings

In general, the SLR International (2001) report was well written and the approaches used in the dose-response modeling and the derivation of the AEL were described in sufficient detail. ICF has conducted a preliminary review of the benchmark dose-response modeling and has identified certain aspects of the SLR benchmark modeling for which a slightly different approach may be preferable. These aspects are described below.

Selection of Models

SLR ran seven models of quantal endpoints. Two of these models were mislabeled--the "logistic model" is actually a log-logistic model, and the model labeled as the "probit model" is actually a log-probit model. ICF suggests that the true logistic and probit models should also be run on quantal data sets. SLR also ran linear and quadratic models on the quantal data sets. Because these models are special cases of the Weibull and multistage models, ICF believes that linear and quadratic models need not be run on the quantal endpoints. For continuous endpoints, SLR performed linear model runs in addition to power and polynomial model runs. Since a linear model run with continuous endpoints is a special case of the power and polynomial models, ICF would choose not to run the linear model separately. It is not expected that these differences in model selection would materially impact the results of the benchmark analysis. It should be noted, however, that the above recommendations regarding the dose-response modeling conducted by SLR are based on a preliminary review of their analysis. A more extensive review could potentially identify additional concerns regarding the SLR dose-response modeling.

Choice of Uncertainty Factors

The authors of the report concluded, based on their investigation, that a BMDL of 156 ppm was recommended to represent the toxicity of nPB in the derivation of the AEL. SLR attempts to justify the use of a single uncertainty factor of 1 to account for interspecies variation, intraspecies variation, exposure duration, and the use of a lowest observed adverse effect level (LOAEL) rather than a no observed adverse effect level (NOAEL). ICF agrees with SLR that an uncertainty factor is not necessary for the use of a LOAEL instead of a LOAEL since a more

sophisticated benchmark dose approach was used. ICF also agrees that there is no need to add an uncertainty factor for exposure duration of the test animals in the two-gneration study. However, ICF disagrees with the decision made by SLR to use an uncertainty factor of 1 for extrapolation from animal data to humans and for the protection of sensitive populations.

The authors of the SLR report correctly indicate that in the extrapolation from animal data to humans, it is assumed that humans are always more sensitive than the animal model. The authors of the SLR report contend that an uncertainty factor of 1 is sufficient for the extrapolation from animals to humans for NPB. This assertion is based on the results of *in vitro* studies conducted with NPB where cytoxicity, enzyme levels (indicative of cell stress), and DNA repair were measured. *In vitro* data are often useful in discerning the mode of action by which a chemical may induce a toxic effect. In some cases, the mode of action that is operative in the animal model may not be operative in humans; alternatively, quantitative adjustments may be included in consideration of differences in sensitivity. The authors, however, provide no evidence that the findings in the *in vitro* studies are relevant to the critical effects observed *in vivo* (liver and reproductive toxicity). Moreover, the cytotoxicity testing was conducted with a human hepatoma cell line. Although these data indicate the possibility that human and rodent liver cells might react similarly in their response to NPB exposure, the SLR report does not provide data indicating that this is the case . Also, it is unclear from the report if responses observed in a tumor cell line would be predictive of responses in normal hepatic cells (i.e., nontransformed cells) or spermatic cells. Therefore, ICF finds there is not sufficient data to support SLR's conclusions that an uncertainty factor of 1 is appropriate for animal-to-human extrapolation.

SLR also notes that the concentration at which cytoxicity was observed in the *in vitro* assays (500 ppm) was comparable with the air concentrations at which effects were reported in the animal studies. Based on this observation, SLR concluded that animal exposure to ambient air concentrations of 500 ppm NPB during an inhalation toxicity study would be expected to produce a response. It is unclear how this conclusion was reached, given that exposures to an air concentration would not result in the same concentration at the target tissue. Finally, SLR concludes that the developing fetus would have the same sensitivity as the mother and a safety factor would not be necessary. Given that there is no suggestion in the report that NPB is a developmental toxicant, it was unclear why this argument was made. *{Also, isn't this inconsistent with the CERHR findings? Which report is "the report"–SLR's?}* Further, given that no pharmacokinetic or pharmacodynamic data for transplacental exposure were presented in the report, and no such data regarding this endpoint following exposure of humans or animals to NPB exist in the published literature, it is unclear how that statement could be justified.

With regard to the protection of sensitive individuals, SLR correctly states that workplace exposures are typically incurred by healthy individuals and sensitive subpopulations are generally not involved. SLR presents an argument in which the results of the *in vitro* studies discussed above were compared to the results of the animal *in vivo* toxicity studies. ICF agrees that the typical worker population is considered to consist of healthy individuals and that using an uncertainty factor to account for the protection of sensitive individuals is not necessary in most cases. Incorporating a factor to account for sensitive individuals may be advisable, however, depending on the toxicity of the chemical and the endpoint in question. In the case of NPB, it is possible that an otherwise healthy worker could have an undiagnosed medical condition (e.g., a

low number of motile sperm) that would cause him to be more susceptible to the effects of NPB. Consequently, this should be considered in the application of uncertainty factors.

Conclusions

The report generated by SLR consisted of benchmark dose-response modeling of approximately 60 data sets from the animal toxicity studies that have been conducted with NPB. Based on our preliminary review, ICF noted a few minor concerns relevant to the benchmark modeling. First, ICF believes an adjustment should be made to correct for differences in exposure between experimental animals and workers in an occupational environment. Further, ICF considered the arguments put forth by SLR regarding the use of uncertainty factors inadequate to justify the use of a single overall uncertainty factor of 1. In particular, the justification provided by SLR for the use of a factor of 1 for the extrapolation from animals to humans and for the use of a factor of 1 for the protection of sensitive individuals was not compelling for the reasons listed above. ICF recommends that in the derivation of an AEL for NPB, an uncertainty factor of 3 should be used to account for the extrapolation from animals to humans and an additional uncertainty factor of 2-3 should be used for the protection of sensitive individuals.

Reference

SLR International Corp. 2001. Inhalation occupational exposure limit for n-propyl bromide. SLR International Corp. Concord, California. July 17.